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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/645,706	08/24/2000	Keith V. Wood	341.005US1	3329

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EXAMINER	
PROUTY, REBECCA E	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/645,706	WOOD ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11,12,14,15,18,20,21,24-39,41-45,47,60-64,67 and 68* is/are pending in the application.

4a) Of the above claim(s) *64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11,12,14,15,18,20,21,24-39,41-45,47,60-63,67 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/03 & 8/03*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claims 10, 13, 16, 17, 19, 22, 23, 40, 46, 48-59, 65 and 66 have been canceled. Claims 1-9, 11, 12, 14, 15, 18, 20, 21, 24-39, 41-45, 47, 60-64 and newly presented claims 67 and 68 are still at issue and are present for examination.

Applicants' arguments filed on 8/14/03, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim 64 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 11/18/02.

Claims 1-9, 11, 12, 14, 15, 18, 20, 21, 24-39, 41-45, 47, 60-63, 67, and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 (from which claims 2-9, 11, 12, 14, 15, 18, 20, 21, 24-39, 41-45 and 60-62 depend), 47, 63, 67 and 68 are vague and indefinite in the recitation of "transcription regulatory sequences composition", "a reduced number of transcription factor binding sequences" and/or "a reduced number of intron splice

sites, poly(A) addition sites and promoter sequences" as without knowing all the possible sequences which are considered to be transcriptional regulatory sequences, transcription factor binding sequences, intron splice sites, poly(A) addition sites and promoter sequences such a calculation is impossible as one could never obtain a count of the number of such sequence in any reference nucleic acid. While there are clearly art defined specific sequences within each of these categories, each of them is an open-ended group of sequences which includes many unknown members. Clearly while many transcription factors and their associated binding sequences are known in the art, new members are being added frequently such that the scope of the claims would change.

Applicants argue that for any given set of possible sequence motifs, by random chance alone, a particular sequence would likely contain transcriptional regulatory sequences, and the average occurrence of those sequences within a coding region could be readily determined either manually or via computer. This is not persuasive because while this is true for any given set of sequences, in the instant case, the set of sequences which is to be used is not defined.

Claims 1-6, 14, 15, 20-21, 24-33, 35-39, 41-45, 47, 54, 60, 61, 63, 67 and 68 are rejected under 35 U.S.C. 112, first

paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is explained in the previous Office Action.

Applicants argue that the specification provides a detailed description of the preparation of synthetic nucleic acid molecules having codon modifications which result in RNA having improved translatability in a particular host cell and decreased transcriptional regulatory sequences, i.e., modifications which result in enhanced transcription of a synthetic DNA molecule, and so reflect changes which occur during natural selection. This is not persuasive because while the specification provides detailed disclosure for the alteration of codons to improve translatability in a particular host cell and to decrease the presence of transcriptional regulatory sequences without altering the sequence of the encoded protein and thus its function, the rejected claims recite a genus of nucleic acids with not only these types of alterations but including many alterations in the sequence of the encoded protein as well (up to 15% of the sequence). The specification does not provide a sufficient description for this claimed genus as the specification does not teach any representative species of nucleic acids with

alterations in the encoded protein sequence and this genus will be highly variable in function as the alterations in the protein sequence will unpredictably alter the function of the wild type protein.

Claims 1-6, 14, 15, 20-21, 24-33, 35-39, 41-45, 47, 60, 61, 63, 67 and 68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant of a parent DNA molecule encoding a polypeptide identical to a polypeptide encoded by said parent DNA, having more than 25% of the codons altered and having a reduced number of transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9 under high stringency conditions and encode a polypeptide having luciferase activity, does not reasonably provide enablement for any variant DNA molecules encoding a polypeptide having at least 85% identity to a wild type polypeptide, having more than 25% of the codons altered and having reduced number of transcription regulatory sequences than the parent nucleic acid or to any nucleic acid which will hybridize to SEQ ID NO:9 under medium stringency conditions, encode a protein having 85% identity to the polypeptide encoded by SEQ ID NO:9, have more than 25% of the codons altered and have a reduced number of transcription regulatory sequences. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicants argue that it is well within the skill of the art worker to prepare a nucleic acid molecule encoding a polypeptide having at least 85% identity to a reference polypeptide, which nucleic acid molecule has an altered codon composition and optionally other altered sequences and that it is well within the skill of the art to selectively or randomly substitute amino acids in a particular protein and screen the resulting mutated proteins for a desired activity. However, this is not persuasive as applicants arguments are all relevant only to whether the specification is enabling for making the scope of the claimed invention. However, the rejection is applied because the specification does not teach how to **use** the scope of the claimed invention without undue experimentation. Applicants claims encompass **all** nucleic acids with 85% identity to **any** nucleic acid of interest in which the codon preference has been altered. The claims encompass all variants, those the retain the function of the parent nucleic acid, those that lose all function, and those that alter the function in any manner at all. The specification

clearly does not teach how one of skill in the art could use the scope of variants claimed. While as noted a skilled artisan could easily determine if any variant retained the function of the parent nucleic acid, the vast majority of nucleic acids encoding a polypeptide with 85% identity to a parent polypeptide of interest will **not** encode a polypeptide which retains the function of the parent polypeptide. It is well established in the art that the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein, that any tolerance to modification for a given protein diminishes with each further and additional modification and that the result of modifications to the sequence is unpredictable. Thus as here where the claims allow up to 15% of the sequence of the parent protein to be altered, the overwhelming majority of the claimed variants will not be useful in the same manner as the parent polypeptide and the specification fails to teach how to use these variants.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

> skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, 12, 14, 15, 20, 21, 24-39, 41-45, 60-63 and 67-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Sherf et al. (US Patent 5,670,356) in view of Zolotukhin et al. (US Patent 5,874,304) and Iannacone et al. The rejection is explained in the previous Office Action.

Applicants point out the elements that are lacking in each of the three references cited within the rejection and conclude with a statement that none of the references alone or in combination teach or suggest a synthetic nucleic acid molecule which has a codon composition and transcription regulatory sequence composition that is different than that of a wild type nucleic acid sequence encoding a polypeptide which has at least 85% sequence identity to the polypeptide encoded by the synthetic nucleic acid molecule, wherein the codons which differ are selected so as to result in the synthetic nucleic acid molecule

having a codon composition differing at more than 25% of the codons from the wild type nucleic acid sequence and having a reduced number of transcription factor binding sequences, or a vector having a modified backbone comprising a synthetic nucleic acid molecule having a reduced number of transcriptional regulatory sequences relative to a vector comprising a parent nucleic acid sequence. However, applicants have not provided any basis for their conclusion that the combination of the three references does not suggest the claimed invention as previously stated by the rejection. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F:2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants further argue that Sherf et al. provide no motivation to further modify any gene to further increase codon substitutions without inadvertently introducing additional transcription regulatory sequences. This is not persuasive because while Sherf et al. may not explicitly suggest further codon substitutions, the combined disclosures of the cited references clearly suggest that alterations of most of the codons of genes which are to be expressed in evolutionarily highly distinct organisms from those in which they evolved (and

fireflies and humans are clearly highly evolutionarily diverse) substantially improve the levels of expression in the new host. Furthermore, one of skill in the art would have had a reasonable expectation of success in view of the results of Zolotukhin et al. and Iannacone et al. who each successfully improved the expression of such a gene by such modification. While it is acknowledged that one cannot be certain that the modifications will have unexpected consequences, applicants are reminded that obviousness does not require an absolute certainty of success but only a reasonable expectation thereof.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the

statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty
Primary Examiner
Art Unit 1652